

# **Update on post-licensure safety monitoring of recombinant zoster vaccine (RZV, Shingrix)**

## **June 2019 Advisory Committee on Immunization Practices (ACIP) meeting**

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## Disclaimer

- The findings and conclusions in this presentation are those of the authors and do not necessarily represent the official position of CDC and FDA
- The use of product trade names is for identification purposes only

# Overview

- Background
- Safety monitoring update  
from the **Vaccine Adverse Event Reporting System (VAERS)**
- Rapid Cycle Analysis (RCA)  
from the **Vaccine Safety Datalink (VSD)**
- FDA assessment of Guillain-Barré syndrome following  
recombinant zoster vaccine from **Medicare** data
- Summary and next steps

# Vaccine safety monitoring and research terms

Term	Explanation
<b>Adverse event</b>	An adverse medical or health event following vaccination (a temporally associated event), which may or may not be related to vaccination (i.e., coincidental).
<b>Adverse reaction</b>	An adverse health event following vaccination where substantial evidence exists to suggest the event is causally related to vaccination.
<b>MedDRA</b>	A clinically-validated international medical terminology used by regulatory authorities to describe health outcomes and events.
<b>ICD-10 and 9</b>	A system used by physicians and other healthcare providers to classify and code diagnoses, symptoms and procedures associated with healthcare.
<b>Automated analysis</b>	Analysis on administrative or claims data or non-chart/health record confirmed data.
<b>Chart confirmed/ medical record confirmed case</b>	A case where review of medical charts and records by physicians or medical personnel confirms the diagnosis as valid and with accurate onset relative to timing of vaccination.
<b>Incident case</b>	A new case occurring for the first time ever or during a specified time period.
<b>Prevalent or non-incident case</b>	A case that has been diagnosed in the past prior to vaccination or prior the study period that has become part of the patient's past medical history and therefore is not new.
<b>Biologically plausible risk interval</b>	The time interval following vaccination where it is biologically plausible, based on the best available science, that an observed adverse event could be related to vaccination.
<b>Statistical signal</b>	A finding from an analysis where a calculated value (i.e., the test statistic) exceeds a specified statistical threshold; a statistical signal does not necessarily represent a vaccine safety problem and requires further assessment before conclusions can be drawn.

# Recombinant Zoster Vaccine (RZV, Shingrix)

- Adjuvanted (AS01<sub>B</sub>) glycoprotein vaccine
- Licensed Oct 2017; preferentially recommended by ACIP for adults ≥50 years
  - Live-attenuated zoster vaccine (ZVL, Zostavax) recommended for adults ≥60 years
- Initial post-licensure safety data presented at the Feb 2019 ACIP meeting
  - Overall, safety profile of RZV consistent with pre-licensure clinical trial data
  - VAERS data indicated systemic signs and symptoms and local reactions were commonly reported; there were no findings of disproportional reporting for any pre-specified outcomes
  - Statistical signal was detected for Guillain-Barré syndrome (GBS) in VSD RCA monitoring based on a small number of GBS cases using automated data
    - Signal assessment in progress, including FDA analysis of Medicare data

# Safety monitoring update

from the **Vaccine Adverse Event Reporting System (VAERS)**



**VAERS**

## Vaccine Adverse Event Reporting System

Co-managed by  
CDC and FDA

<http://vaers.hhs.gov>

Vaccine Adverse Event Reporting System  
[www.vaers.hhs.gov](http://www.vaers.hhs.gov)

[About VAERS](#)
[Report an Adverse Event](#)
[VAERS Data](#)
[Resources](#)
[Submit Follow-Up Information](#)

Have you had a reaction following a vaccination?

1. Contact your healthcare provider.
2. [Report an Adverse Event](#) using the VAERS online form or the new downloadable PDF. *New!*

**Important:** If you are experiencing a medical emergency, seek immediate assistance from a healthcare provider or call 9-1-1. CDC and FDA do not provide individual medical treatment, advice, or diagnosis. If you need individual medical or health care advice, consult a qualified healthcare provider.

¿Ha tenido una reacción después de recibir una vacuna?

1. Contacte a su proveedor de salud.
2. [Reporte una reacción adversa](#) utilizando el formulario de VAERS en línea o la nueva versión PDF descargable. *Nuevo!*

What is VAERS?

REPORT AN ADVERSE EVENT

Report significant adverse events after vaccination.

SEARCH VAERS DATA

Download VAERS Data and search the CDC WONDER database.

REVIEW RESOURCES

Find materials, publications, learning tools, and other resources.

SUBMIT FOLLOW-UP INFORMATION

Upload additional information related to VAERS reports.

# Vaccine Adverse Event Reporting System (VAERS)

## Strengths

- National data
- Accepts reports from anyone
- Rapidly detects safety signals
- Can detect rare adverse events
- Data available to public

## Limitations

- Reporting bias
- Inconsistent data quality and completeness
- Lack of unvaccinated comparison group
- Generally cannot assess causality

- VAERS accepts all reports from all reporters without making judgments on causality, irrespective of clinical seriousness
- As a hypothesis generating system, VAERS identifies potential vaccine safety concerns that can be studied in more robust data systems



# Methods: VAERS monitoring and analysis

- Descriptive analysis of RZV reports from October 2017 through April 2019 (as of May 10, 2019 )
  - Signs, symptoms, and diagnoses coded using Medical Dictionary for Regulatory Activities (MedDRA) terms
- Reporting rates (based on 11.89 million RZV doses distributed for the U.S. market through March 2019, courtesy GSK)\*
- Empirical Bayesian data mining to detect disproportional reporting for vaccine-adverse event pairings
- Clinical review of reports (includes medical records when available):
  - 20 pre-specified outcomes

\*Reporting rates are adjusted using reports and RZV doses distributed through March 31, 2019

## Pre-specified outcomes (based on pre-licensure trials and ZVL reports)

- Acute myocardial infarction
- Amyotrophic lateral sclerosis
- Anaphylaxis
- Autoimmune disorders
- Autoimmune vasculitis
- Bell's Palsy
- Co-administration with another adjuvanted vaccine
- Death
- Gout
- Guillain-Barré syndrome
- Immune thrombocytopenia
- Inflammatory eye disease
- Lymphadenitis
- Meningitis
- Optic ischemic neuropathy
- Osteonecrosis
- Post-herpetic neuralgia
- Seizures / convulsions
- Stroke / CVA
- Supraventricular tachyarrhythmias

# Reports to VAERS following RZV

- **Reporting rates** *(based on 11.89 million doses distributed through March 2019 and reports through March 2019)*
  - All reports: 154.3 per 100,000 doses distributed
  - Serious reports<sup>\*</sup>: 3.9 per 100,000 doses distributed

<sup>\*</sup>Based on the Code of Federal Regulations if one of the following is reported: death, life-threatening illness, hospitalization or prolongation of hospitalization or permanent disability (FDA routinely reviews all serious reports)

Report characteristics	N (%)
<b>Total reports</b>	18,418
Female	12,431 (67.5)
Non-serious	17,919 (97.3)
<b>Type of reporter</b>	
Manufacturer	6639 (36.0)
Healthcare professional	6372 (34.6)
Patient	4347 (23.6)
Other	1060 (5.8)
<b>Age groups (years)</b>	
<50 <sup>†</sup>	92 (0.5)
50-59	3759 (20.4)
60-69	6385 (34.7)
70-79	4019 (21.8)
80+	1111 (6.0)
Not reported or unknown	3052 (16.6)
<b>RZV given alone</b>	17,363 (94.3)

<sup>†</sup>RZV not approved for use in <50 y/o

# Most common signs and symptoms in reports to VAERS following RZV and review of pre-specified outcomes

Signs and symptoms (MedDRA Preferred Terms)*	18,418 total reports n (%)
Pyrexia (fever)	4625 (25.1)
Chills	3959 (21.5)
Injection site pain	3798 (20.6)
Pain	3731 (20.3)
Headache	3497 (19.0)
Fatigue	3007 (16.3)
Pain in extremity	2986 (16.2)
Injection site erythema	2967 (16.1)
Myalgia	2208 (12.0)
Injection site swelling	2051 (11.1)

- Systemic signs and symptoms and injection site reactions were the most commonly reported AEs
- No unexpected patterns detected by physician reviewers of reports of pre-specified outcomes

\*Not mutually exclusive; a report may contain more than one MedDRA Preferred Term

# Data mining

- Empirical Bayesian (EB) data mining identifies AEs that are reported more frequently than expected, adjusting for age, sex, and the year in which reports are received
  - Identifies AEs that are reported at least twice as frequently as would be expected by chance following a given vaccine (i.e., lower bound of the 90% confidence interval surrounding the EB geometric mean [EB05] >2)
- One empirical Bayesian data mining finding to date for RZV for the MedDRA PT:
  - **“Product administered to patient of inappropriate age”** when looking at individuals aged 19-44.9 years old

## Summary of VAERS review of RZV reports

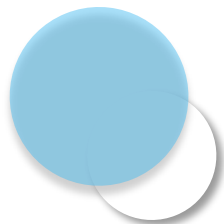
- RZV post-licensure safety monitoring findings in VAERS are generally consistent with the safety profile observed in pre-licensure clinical trials
- Self-limited systemic signs and symptoms and injection site reactions were the most commonly reported adverse events
- Serious adverse events were rarely reported (2.7% of reports; similar to other vaccines given in same age group)
- No empirical Bayesian data mining findings for any RZV-AE pairings except for **“Product administered to patient of inappropriate age”**

# **Rapid Cycle Analysis (RCA)**

from the **Vaccine Safety Datalink (VSD)**

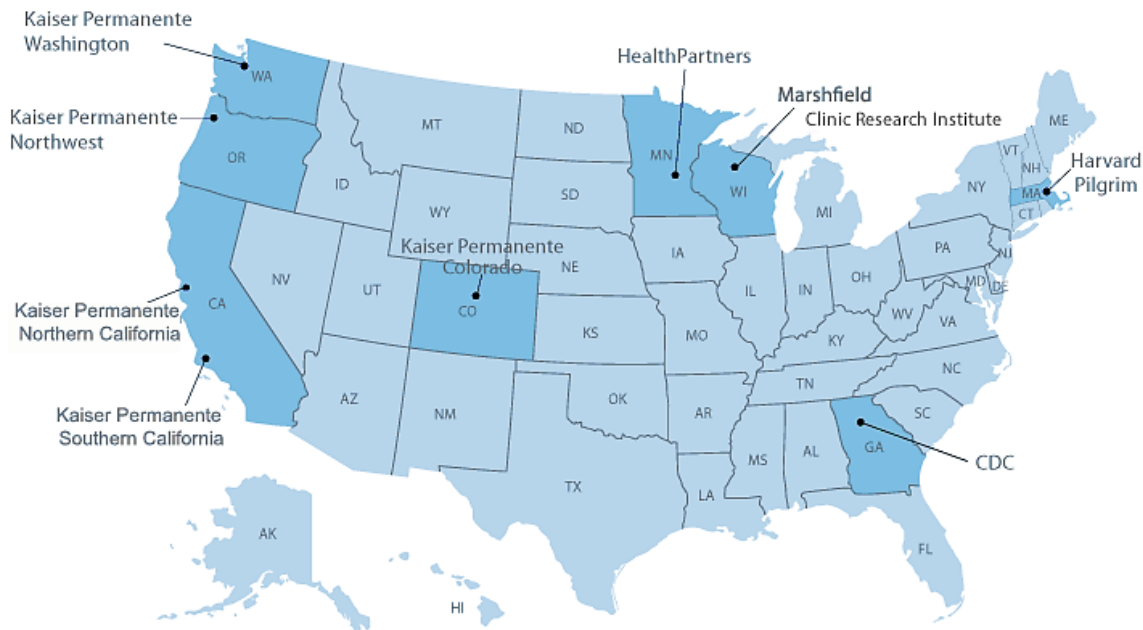


# VSD



**Vaccine  
Safety  
Datalink**

**8** participating integrated  
healthcare organizations

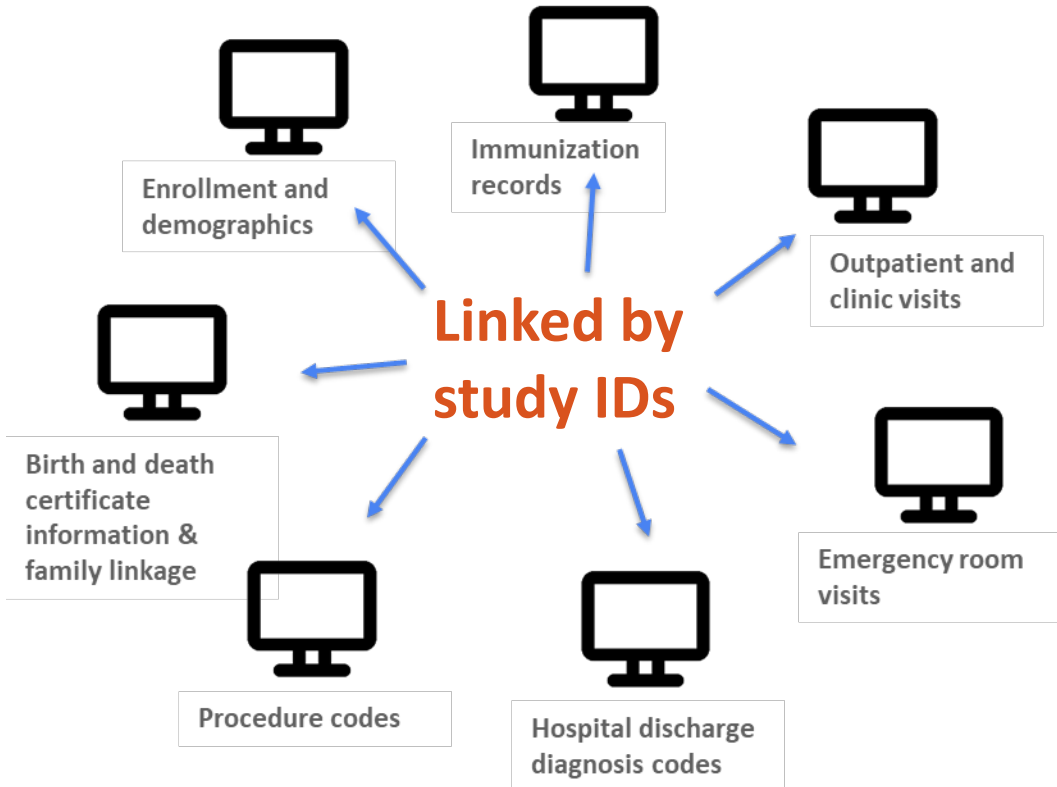




## Vaccine Safety Datalink (VSD)

- Established in 1990
- Collaboration between CDC and several integrated healthcare organizations
- Medical care and demographic data on over 12.1 million persons per year (~3.7% of U.S. population)
- Links vaccination data to health outcome data
- Used for surveillance and research

# VSD electronic files + chart review



+



# Rapid Cycle Analysis (RCA) in VSD

## **A powerful and sophisticated tool**

- Near real-time vaccine-safety monitoring (using sequential monitoring techniques)
- Employs an automated analysis that uses ICD-coded diagnoses from administrative data
- A surveillance activity (signal detection and signal refinement), which is not the same as an epidemiologic study (signal evaluation, causality assessment)
- Requires careful thought and customization in the design, set-up, interpretation

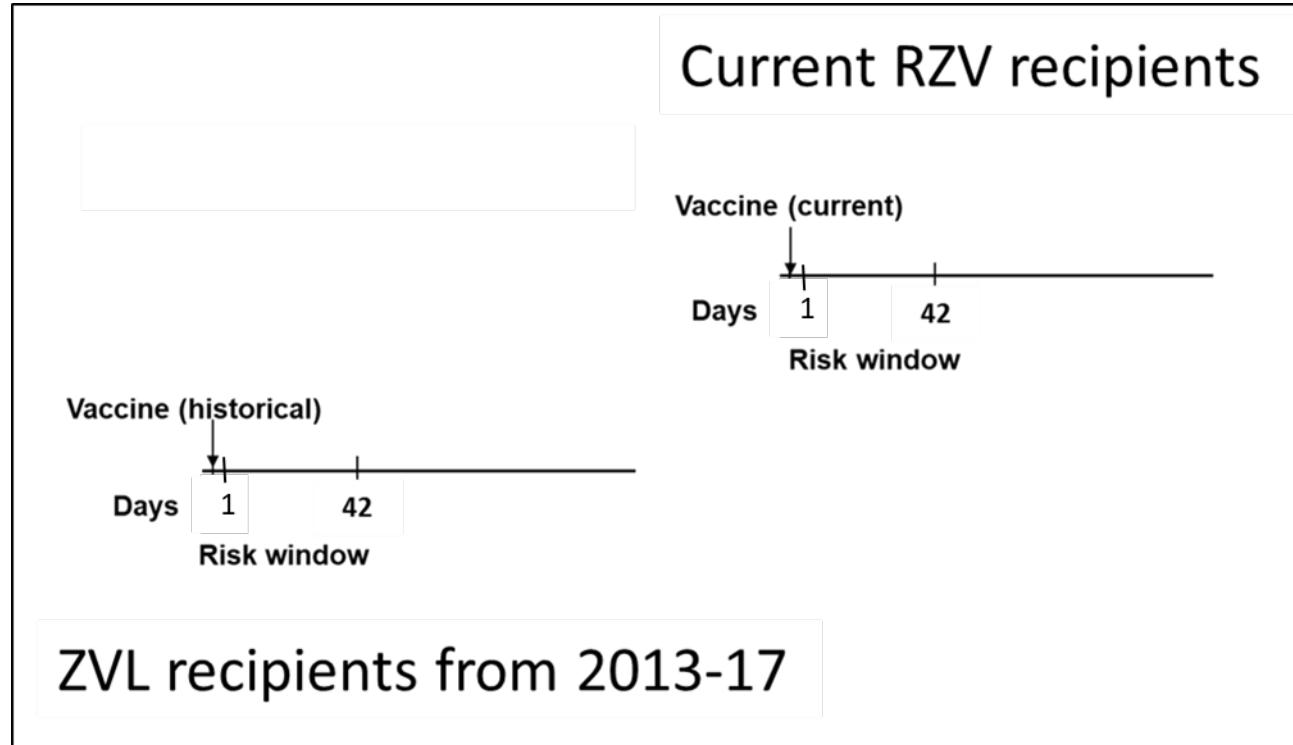
## **Designed to detect statistical signals** (values above specified statistical thresholds)

- When a statistical signal occurs, CDC conducts a series of evaluations using traditional epidemiologic methods
- Chart-confirmation of diagnoses to confirm or exclude cases as true incident cases is a key part of statistical signal assessment

## **Not all statistical signals represent a true increase in risk for an adverse event**

# Primary analysis for RZV RCA\* is a historical comparator design

- Monthly near real-time sequential monitoring of pre-specified outcomes
- Uses ICD-10/9 coded diagnoses
- 18 planned monthly analyses (1<sup>st</sup> at 6 months), with an 18 week data lag
- Presenting interim results of the **7<sup>th</sup> analysis**
- **Test statistic:** Adjusted likelihood ratio test ( $H_0: RR=1$  versus  $H_A: RR>1$ )



## 10 high priority pre-specified RZV RCA outcomes\*

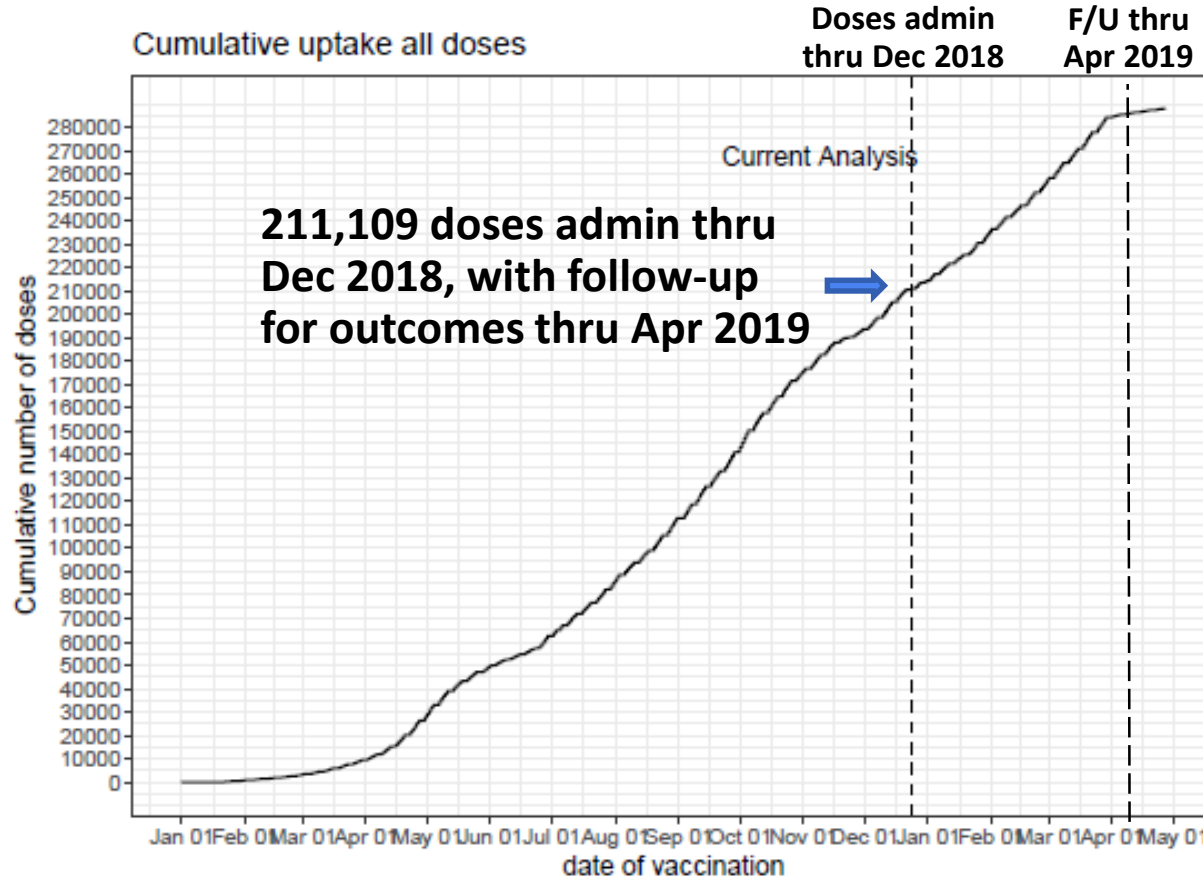
High priority pre-specified outcomes	Risk interval in days
Acute myocardial infarction	1-42
Anaphylaxis	0-1
Bell's palsy	1-42
Convulsion	1-42
Giant cell arteritis	1-42
Guillain-Barré syndrome	1-42
Optic ischemic neuropathy	1-42
Polymyalgia rheumatica	1-42
Stroke	1-42
Supraventricular tachycardia	1-42

\*Other outcomes for descriptive analysis only include: gout, keratitis, non-specific adverse effects, stroke subtypes, pneumonia, keratitis, uveitis and retinitis, zoster ocular disease, systemic reactions, local reactions, urgent care or emergency department visits

## Secondary analyses for RZV RCA uses 2 concurrent comparators

1. Had an ICD-10 coded well-visit during RZV uptake period
2. Received another vaccine (not influenza – e.g., PPSV23, PCV13, Td, Tdap, etc.) during RZV uptake period

# Results: RZV uptake at VSD sites for 7<sup>th</sup> analysis



## RZV RCA results: statistical signals for Bell' palsy and GBS detected

High priority outcomes	Obs events	Exp events	Obs rate (per 100K)	RR	Statistical signal (which analysis)
Stroke	109	126	51.6	0.87	No
Acute MI	106	125	50.2	0.85	No
Polymyalgia rheumatic	35	53	16.6	0.66	No
Supraventricular tachycardia	34	42	16.1	0.82	No
Convulsion assoc. terms	45	40	21.3	1.11	No
Bell's palsy <sup>1</sup>	40	31	18.9	1.31	Yes (at #5)
Anaphylaxis	7	5	3.3	1.32	No
Giant cell arteritis	10	17	4.7	0.61	No
Optic ischemic neuropathy	14	17	6.6	0.83	No
Guillain-Barré syndrome (GBS) <sup>2</sup>	5	1.6	2.4	3.18	Yes (at #2)

<sup>1</sup>Bell's palsy signaled **at 5<sup>th</sup> analysis** (36 obs events vs. 24 exp; RR=1.51, adjusted p=0.03)

<sup>2</sup>GBS signaled **at 2<sup>nd</sup> analysis** (3 obs events vs. 0.6 exp; RR=5.25, adjusted p=0.02)



# Bell's palsy

statistical signal assessment

# Bell's palsy signal assessment in VSD

- RCA statistical signal **at 5<sup>th</sup> analysis**: RR=1.51 (36 obs vs. 24 exp events, p=0.03)
- **At 7<sup>th</sup> analysis**, attenuated somewhat: RR=1.31 (40 obs vs. 31 exp events)
- RRs not consistently elevated for concurrent comparator groups
  - Well-visits RR=0.98, other non-influenza vaccine recipients RR=0.74
- Chart review adjudication performed on the 36 RZV cases (from 5<sup>th</sup> analysis)
  - 21 cases ruled out (11 prevalent/non-incident; 5 miscoded; 2 diagnosis overturned; 3 outside 1-42 day risk window)
  - 15 definite cases with onset within 1-42 day window

# VAERS reports of Bell's palsy following RZV (Oct 2017-Apr 2019)

- No empirical Bayesian data mining finding for RZV-Bell's palsy
- Proportional Reporting Ratio analysis did not detect any disproportional reporting for RZV-Bell's palsy when ZVL, IIV or PPSV23 vaccines were used as comparators
- 59 reports had a MedDRA PTs for Bell's palsy or facial paralysis assigned; upon review:
  - 10 case reports met Brighton criteria for Bell's palsy: level 1 (4), level 2 (0), level 3 (6)
  - 6 case reports did not meet Brighton criteria or had insufficient information, but were explicitly described as physician-diagnosed Bell's palsy
  - 43 case reports did not meet Brighton criteria and were not physician diagnosed
- Of the 16 cases that met Brighton criteria level 1-3, or were physician diagnosed:
  - 14 had symptom onset w/in a 0-42 day risk window following RZV (1 w/concurrent IIV)
    - Translates to reporting rate of **1.2 Bell's palsy cases per million RZV doses distributed\***

\*Reporting rates are adjusted using reports and RZV doses distributed through March 31, 2019

# Guillain-Barré syndrome (GBS)

statistical signal assessment

## RZV RCA results: statistical signals for Bell' palsy and GBS detected

High priority outcomes	Obs events	Exp events	Obs rate (per 100K)	RR	Statistical signal (which analysis)
Stroke	109	126	51.6	0.87	No
Acute MI	106	125	50.2	0.85	No
Polymyalgia rheumatic	35	53	16.6	0.66	No
Supraventricular tachycardia	34	42	16.1	0.82	No
Convulsion assoc. terms	45	40	21.3	1.11	No
Bell's palsy	40	31	18.9	1.31	Yes (at #5)
Anaphylaxis	7	5	3.3	1.32	No
Giant cell arteritis	10	17	4.7	0.61	No
Optic ischemic neuropathy	14	17	6.6	0.83	No
Guillain-Barré syndrome (GBS) <sup>1</sup>	(5)	1.6	2.4	3.18	Yes (at #2)

<sup>1</sup>GBS signaled **at 2<sup>nd</sup> analysis** (3 obs events vs. 0.6 exp; RR=5.25, adjusted p=0.02); at 7<sup>th</sup> analysis, 5 observed ICD-10 coded GBS cases following RZV

## GBS statistical signal assessment in VSD

- Chart review of the 5 ICD-10 coded GBS cases following RZV
  - ❌ Case ruled out: prior diagnosis of GBS, no recurrence or exacerbation after RZV, not a true incident case
  - ❌ Case ruled out: prior diagnosis of GBS, no recurrence or exacerbation after RZV, not a true incident case
  - ❌ Case ruled out: GBS symptom onset prior to vaccination
  - ✅ Confirmed case: Brighton Criteria\* level 2 GBS case with onset in risk window, also received simultaneous PCV13
  - ✅ Confirmed case: Brighton Criteria level 3 GBS case with onset in risk window, probable respiratory infection prior to GBS symptom onset

\*Sejvar et al. Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2011;29(3):599-612.

## GBS statistical signal assessment in VSD (cont.)

- Chart review of the 5 total ICD-9/10 coded GBS cases in the historical ZVL comparator
  - ❌ Case ruled out: prior diagnosis of GBS, no recurrence or exacerbation after RZV, not a true incident case
  - ❌ Case ruled out: upon chart review, case given alternative diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP)
  - ? Unable to confirm case: medical records not available
  - ✓ Confirmed case: Brighton Criteria\* level 2 GBS case with onset in risk window
  - ✓ Confirmed case: Brighton Criteria level 2 GBS case with onset in risk window

\*Sejvar et al. Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2011;29(3):599-612.

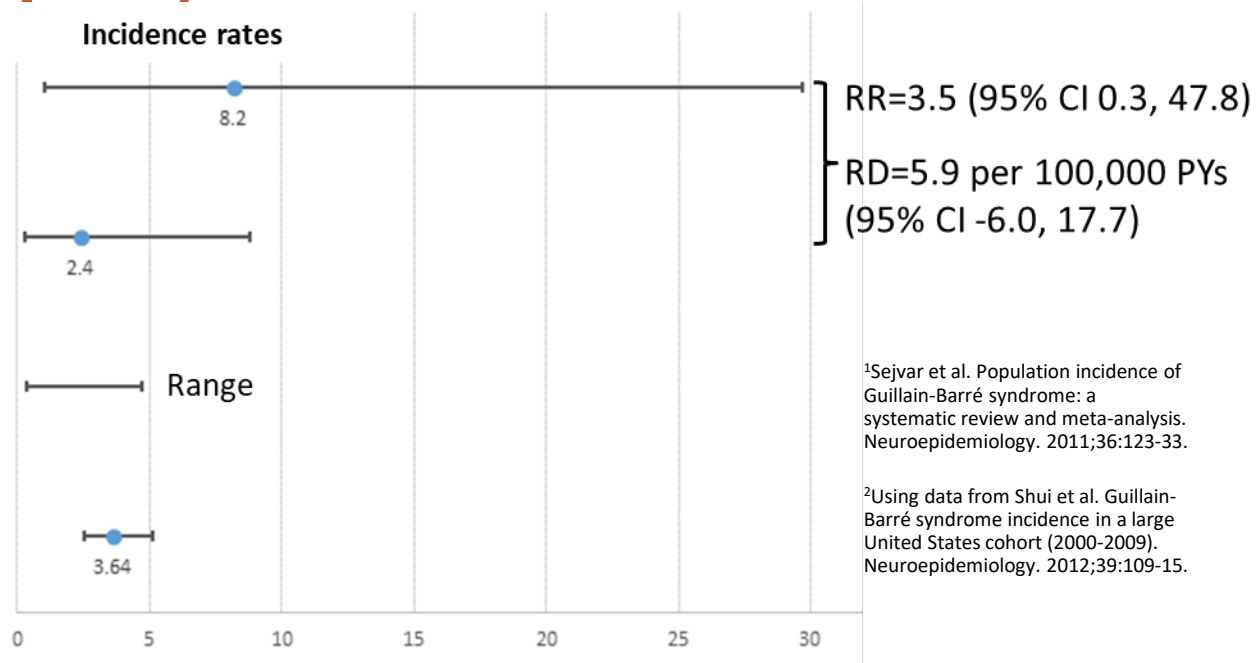
# Comparison of GBS incidence rates in 50+ y/o (per 100K person years)

Chart confirmed GBS IR in VSD **RZV cohort**  
(point estimate, 95% CI) based on 2 cases

Chart confirmed GBS IR in historical VSD  
**ZVL cohort** (point estimate, 95% CI)  
based on 2 cases

Range of GBS IRs from systematic review  
and meta-analysis<sup>1</sup>

GBS IR from data from VSD analysis,  
2000-2009 (point estimate, 95% CI)<sup>2</sup>



- To date, the estimated VSD chart confirmed GBS rate in the current RZV cohort is higher than in the historical ZVL cohort and higher than published estimates in the literature<sup>1,2</sup>
- Uncertainty around the VSD estimated GBS rate following RZV is large, IR=8.2 (95% CI 1.0, 29.7), and overlapping with the background rates reported in the literature



## GBS statistical signal assessment in VSD

- Chart review of the 5 total ICD-9/10 coded GBS cases in the historical ZVL comparator

❌ Case ruled out: prior diagnosis of GBS, no recurrence or exacerbation after RZV, not a true incident case

❌ Case ruled out: upon chart review, case given alternative diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP)

Sensitivity analysis: include this as a true case



? Unable to confirm case: medical records not available

✓ Confirmed case: Brighton Criteria\* level 2 GBS case with onset in risk window

✓ Confirmed case: Brighton Criteria level 2 GBS case with onset in risk window

\*Sejvar et al. Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2011;29(3):599-612.

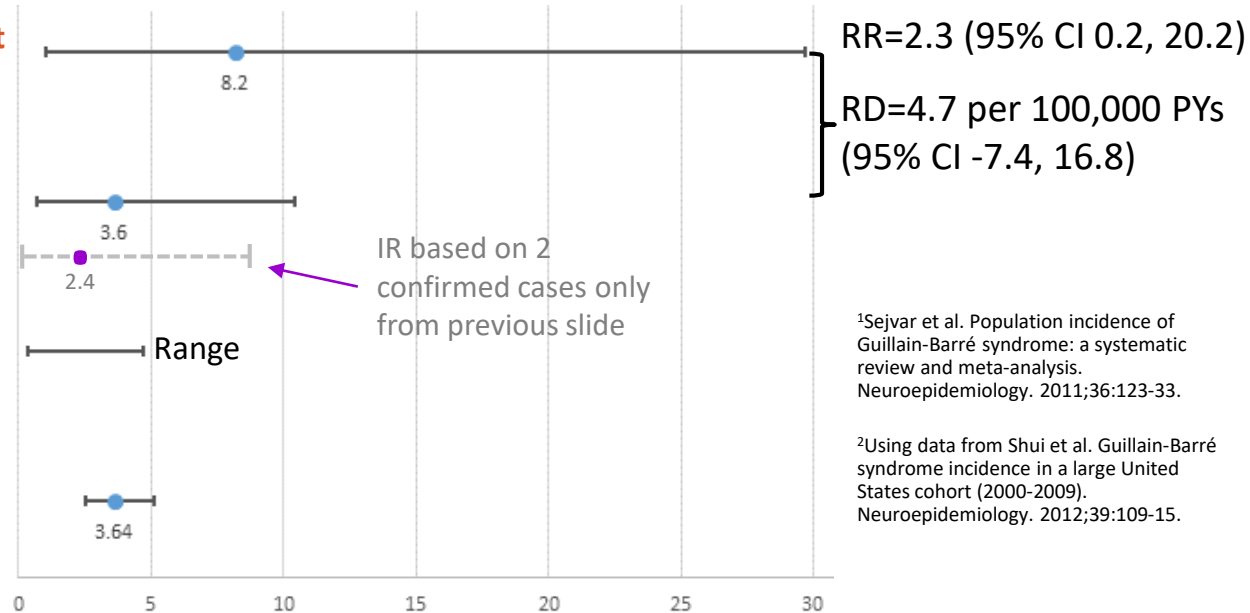
# Sensitivity analysis: comparison of GBS incidence rates in 50+ y/o (per 100K person years)

Chart confirmed GBS IR in VSD **RZV cohort** (point estimate, 95% CI) based on 2 cases

GBS IR in historical VSD **ZVL cohort** (point estimate, 95% CI) based on **3 cases** (**includes unconfirmed case**)

Range of GBS IRs from systematic review and meta-analysis<sup>1</sup>

GBS IR estimate from VSD analysis 2000-2009 (point estimate)<sup>2</sup>



<sup>1</sup>Sejvar et al. Population incidence of Guillain-Barré syndrome: a systematic review and meta-analysis. *Neuroepidemiology*. 2011;36:123-33.

<sup>2</sup>Using data from Shui et al. Guillain-Barré syndrome incidence in a large United States cohort (2000-2009). *Neuroepidemiology*. 2012;39:109-15.

- Including unconfirmed GBS case in the historical ZVL cohort as a true incident case (3 total cases):
  - ZVL vaccinated IR increases from: IR=2.4 (95% CI 0.3, 8.6) to IR 3.6 (95% CI 0.7, 10.4)
  - RR decreases from: RR=3.5 (95% CI 0.3, 47.8) to RR=2.3 (95% CI 0.2, 20.2)
  - RD decreases from: RD=5.9 per 100K PYs (95% CI -6.0, 17.7) to RD=4.7 per 100K PYs (95% CI -7.4, 16.8)

# VAERS reports of GBS following RZV (Oct 2017-Apr 2019)

- No empirical Bayesian data mining finding for GBS
- Proportional Reporting Ratio analysis did not detect any disproportional reporting for RZV-GBS when either ZVL, IIV or PPSV23 vaccines were used as comparators
- 46 reports had a MedDRA Preferred Term for GBS assigned; upon review:
  - 24 case reports met Brighton criteria for GBS: level 1 (2), level 2 (17), level 3 (5)
    - 2 described URI/ILI symptoms 2-3 weeks before GBS
  - 7 case reports did not meet Brighton criteria or had insufficient information, but were explicitly described as physician-diagnosed GBS
  - 15 case reports did not meet Brighton criteria and were not physician diagnosed
- Of the 31 cases that met Brighton criteria level 1-3, or were physician diagnosed:
  - 29 had symptom onset w/in a 0-42 day risk window following RZV (1 w/concurrent IIV)
    - Translates to reporting rate of **2.4 GBS cases per million RZV doses distributed\***

\*Reporting rates are adjusted using reports and RZV doses distributed through March 31, 2019

# **FDA assessment of Guillain-Barré syndrome following recombinant zoster vaccine (RZV)**

from Medicare data



## **FDA assessment of the risk of Guillain-Barré syndrome (GBS) following recombinant zoster vaccine (RZV) in Medicare data**

Slides and content courtesy Rich Forshee, PhD

# Background

- Upon detection of the statistical signal for GBS following RZV in the VSD RCA in the fall of 2018, CDC consulted with FDA on the possibility of additional analyses in other databases
- Subsequently, FDA in collaboration with CDC and CMS initiated an assessment of risk of GBS following RZV in Medicare data
- Interim results of an automated (ICD-coded) analysis are available
- Additional work to refine the analysis is in progress

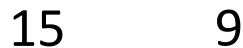
# Methods

- Replication of signaling VSD analysis
  - Cohort comparison of the post-vaccination GBS rate between a vaccinated RZV population and a historical vaccinated ZVL population
- Population
  - Exposure: Vaccinations identified using National Drug Codes (NDCs) in Part D
    - RZV vaccination window: Oct 2017 – Dec 2018
    - ZVL vaccination window: Oct 2012 – Sep 2017
  - Aged into Medicare (65 years or older)
  - Continuous enrollment in Medicare Parts A, B and D for 365 days prior to vaccination
    - Clean period: No GBS in 365 days prior to vaccination date

# Methods

- Risk window: Days 1-42 post-vaccination
- Outcome: Primary inpatient Guillain-Barré syndrome (GBS) diagnosis
  - ICD-9: 357.0
  - ICD-10: G61.0
- Poisson model:  $\log(E(Y|X)) = \beta_0 + \beta_1 * Vaccine + \beta_2 * X + \log(t)$ 
  - Y = GBS outcome variable*
  - Vaccine = Binary vaccine cohort term (Shingrix vs. Zostavax)*
  - X = Covariates*
  - t = exposure time*





# GBS outcome rates and model results

Cohort	ICD-coded GBS cases	Eligible doses	Total person time (100,000 person-days)	Outcome rate (per 100,000 person-days)	Rate ratio (95% CI) adjusted for age and sex
RZV vaccinated	15	1,318,004	514.9	0.029	<b>2.34 (1.01, 5.41)</b> p=0.047
ZVL vaccinated	9	1,817,099	753.4	0.012	---

$$\text{Rate ratio} = \frac{\text{GBS rate in RZV vax}}{\text{GBS rate in ZVL vax}}$$

# GBS outcome rates and model results (cont.)



<b>Cohort</b>	<b>ICD-coded GBS cases</b>	<b>Eligible doses</b>	<b>Outcome rate</b> (per million doses)	<b>Rate ratio (95% CI)*</b> adjusted for age and sex	<b>Attributable risk (95% CI)</b> (per million doses) adjusted for age and sex
RZV vax	15	1,318,004	11.38	2.34 (1.01, 5.41)	<b>6.54 (-0.11, 13.9)</b>
ZVL vax	9	1,817,099	4.95	---	---

\*Based on outcome rates of GBS cases per 100,000 person-days

# Summary

- Interim results of the FDA cohort comparison of post-vaccination GBS rate between vaccinated RZV population and historical ZVL population indicate:
  - An elevated adjusted rate ratio=2.34 (95% CI 1.01, 5.41),  $p=0.047$
- Results should be interpreted with caution
  - This is an automated analysis using ICD-coded GBS diagnoses; chart review/confirmation of cases is pending
  - Current vs. historical comparisons are subject to potential confounding and require adjustments, which are in progress
- A chart confirmed self-controlled analysis is planned, which will control for many potential confounders of historical comparator designs

## **Selected secondary outcomes and secondary analyses**

# Secondary outcomes and comparators for RZV RCA

- Descriptive analyses for lower priority outcomes in historical comparator (ZVL) design
  - RR <1: hemorrhagic stroke (0.48) gout (0.84), pneumonia (0.65), zoster ocular (0.63)
  - RR ~1: non-hemorrhagic stroke (0.95), local rxns (0.96), uveitis/retinitis (0.89), urgent care/emergency dept. visit (0.90)
  - RR >1: systemic rxns (1.21), non-specific AE (1.23), and keratitis (1.15)
- Well visit comparators (50+ yo) during RZV uptake period (N=1,415,492)
  - All high priority outcomes RR <1.0 except GBS (RR=1.86; 5 obs vs. 2.7 exp events)
- Other (non-influenza) vaccine recipient comparators (50+ yo) during RZV uptake (N=518,115)
  - All high priority outcomes RR <1.0 except GBS (RR=1.53; 5 obs vs. 3.3 exp events)

**Summary and next steps**

## RZV uptake

- Still in the initial uptake period for RZV and early in the post-licensure monitoring process, considering constraints on supply
  - 11.89 million RZV doses distributed for the U.S. market through March 2019
  - 211,109 RZV doses included in 7<sup>th</sup> (of 18) VSD RCA analysis covering the period Jan-Dec 2018, with outcome monitored through April 2019
  - 1,318,004 RZV doses included in the FDA Medicare data analysis; vaccination window Oct 2017-Dec 2018



## Summary of post-licensure RZV monitoring

- No concerning patterns or findings of disproportional reporting for adverse health events in **VAERS**
- Statistical signals detected for **Bell's palsy** and **GBS** in **VSD RCA** in automated analyses
- Elevated rate ratio for **GBS** detected in the FDA cohort analysis in **Medicare data** using automated analysis

# Summary of post-licensure RZV monitoring (cont.)

## Assessment of statistical signal for Bell's palsy in VSD

- Statistical signal for Bell's palsy in VSD RCA is not consistent across comparators
  - RR=1.31 at 7<sup>th</sup> analysis (attenuated from RR=1.51 at 5<sup>th</sup> [signaling] analysis)
  - RR=0.98 comparing to well-visits
  - RR=0.74 comparing to other non-influenza vaccine recipients
- Ongoing Bell's palsy chart review/confirmation indicates 15 of 36 presumptive cases confirmed in 1-42 day risk window

# Summary of post-licensure RZV monitoring (cont.)

## Assessment of statistical signal for GBS in VSD

- Assessment in VSD has included chart review of all potential GBS cases identified by ICD codes in current RZV and historical ZVL recipients
  - Chart confirmed  $RR=3.5$  (95% CI 0.3, 47.8) based on 2 RZV and 2 ZVL confirmed cases
    - Risk Difference=5.9 per 100,000 PYs (95% CI -6.0, 17.7)
  - If the 'unconfirmed' GBS case in the ZVL comparator group is included as a true incident case,  $RR$  changes to  $RR=2.3$  (95% CI 0.2, 20.2)
    - Risk Difference=4.7 per 100,000 PYs (95% CI -7.4, 16.8)

# Summary of post-licensure RZV monitoring (cont.)

## FDA assessment of GBS risk following RZV from Medicare data

- Interim results of the FDA cohort comparison of post-vaccination GBS rates between vaccinated RZV population and historical ZVL population using ICD-coded cases showed elevated rate ratio

<b>Rate ratio (95% CI)</b> adjusted for age and sex	<b>Attributable risk (95% CI)</b> (per million doses) adjusted for age and sex
2.34 (1.01, 5.41)	6.54 (-0.11, 13.9)

- Additional analysis and chart review/confirmation pending

## Final thoughts and next steps

- Safety profile of RZV is generally consistent with pre-licensure clinical trial data
- Two systems have detected an increased risk for GBS; however, numbers are small in VSD and chart reviews are pending in FDA Medicare analysis
- CDC will continue to monitor GBS (and Bell's palsy) in VSD
  - Track additional cases of GBS, conduct rapid chart review, estimate RR for chart-confirmed GBS over time as more data accumulate, and consider SCRI analysis
  - Track additional cases of Bell's palsy; consider conducting chart review for cases following ZVL to estimate a chart-confirmed RR at end of surveillance period
- FDA is in the process of accessing charts to review GBS cases in the Medicare cohort analysis and will consider doing a chart confirmed self-controlled analysis to further assess risk of GBS following RZV
- Initial safety monitoring data so far are insufficient to conclude that a safety problem exists for GBS, but further evaluation and continued vigilance are warranted

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# Thank you

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

